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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 20040415

Application Number: 08/398,555
Filing Date: March 03, 1995
Appellant(s): CIMA ET AL.

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 2, 2004.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The amendment after final rejection filed on February 9, 2004 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that (1) claims 14-17 and 33, and (2) claims 32 and 34, do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

4,954,637	Nitecki et al	09-1990
5,171,264	Merrill	12-1992

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5,370,681	Herweck et al	12-1994
5,508,164	Kausch et al	04-1996
5,522,895	Mikos et al	06-1996
5,906,828	Cima et al	05-1999
6,045,818	Cima et al	04-2000

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14-17 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,906,828 and further in view of Nitecki et al, Kausch et al, and Applicants' admission of the prior art at page 12, lines 1-12, of the specification. Although the conflicting claims are not identical, they are not patentably distinct from each other. It is the examiner's position that a one-way test is appropriate for obviousness-type double patenting. The claims of the '828 patent do not recite using the same attachment agent to link the tether to the substrate and the growth effector molecule. Nitecki et al (see, e.g., column 1, line 67 - column 2, line 15) and Kausch et al (see, e.g., column 6, lines 52-67) disclose that homobifunctional coupling agents and linkers are known for purposes of coupling of biological materials and for immobilization, albeit having the disadvantage of intramolecular cross-linking and self-condensation and the loss of a portion of the linker due to reaction of both ends of the linker with the support. It would have been obvious to one of ordinary skill in the art to use the same attachment agent to link the tether to the substrate and the growth effector molecule in the claimed invention of the '828 patent, with only the expected disadvantages arising from the use of homobifunctional rather than

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heterobifunctional coupling agents or linkers, because the claims of the '828 patent require covalent attachment yet are not limited to any particular attachment agents, because it is routine to use standard immobilization chemistries which are well known in the art to achieve only the expected immobilization because of their familiarity and predictability to the artisan, and because Nitecki et al and Kausch et al teach that the use of homobifunctional coupling agents and linkers are known and useful in the art for the same purpose claimed in the '828 patent. The claims of the '828 patent do not recite an attachment agent which is cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, or maleimide. Applicants admit at page 12, lines 1-12, of the specification that cyanogen bromide, succinimide, aldehydes, tosyl chloride, avidin-biotin, epoxide, and maleimides are standard immobilization chemistries which are well known in the art. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to attach the tethers recited in the claimed invention of the '828 patent to the substrate using standard immobilization chemistries which are well known in the art, including cyanogen bromide, succinimide, aldehydes, tosyl chloride, avidin-biotin, epoxide, and maleimides, because the claims of the '828 patent require covalent attachment yet are not limited to any particular attachment agents and because it is routine to use standard immobilization chemistries which are well known in the art to achieve only the expected immobilization because of their familiarity and predictability to the artisan.

Claims 32 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 20 of U.S. Patent No. 6,045,818 and further in view of Nitecki et al, Kausch et al, and Applicants' admission of the prior art at page 12, lines 1-12, of the specification. Although the conflicting claims are not identical, they are not patentably

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distinct from each other. It is the examiner's position that a one-way test is appropriate for obviousness-type double patenting. The claims of the '818 patent do not recite using the same attachment agent to link the tether to the substrate and the growth effector molecule. Nitecki et al (see, e.g., column 1, line 67 - column 2, line 15) and Kausch et al (see, e.g., column 6, lines 52-67) disclose that homobifunctional coupling agents and linkers are known for purposes of coupling of biological materials and for immobilization, albeit having the disadvantage of intramolecular cross-linking and self-condensation and the loss of a portion of the linker due to reaction of both ends of the linker with the support. It would have been obvious to one of ordinary skill in the art to use the same attachment agent to link the tether to the substrate and the growth effector molecule in the claimed invention of the '818 patent, with only the expected disadvantages arising from the use of homobifunctional rather than heterobifunctional coupling agents or linkers, because the claims of the '828 patent require covalent attachment yet are not limited to any particular attachment agents, because it is routine to use standard immobilization chemistries which are well known in the art to achieve only the expected immobilization because of their familiarity and predictability to the artisan, and because Nitecki et al and Kausch et al teach that the use of homobifunctional coupling agents and linkers are known and useful in the art for the same purpose claimed in the '828 patent. The claim of the '818 patent does not recite an attachment agent which is cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, or maleimide. Applicants admit at page 12, lines 1-12, of the specification that cyanogen bromide, succinimide, aldehydes, tosyl chloride, avidin-biotin, epoxide, and maleimides are standard immobilization chemistries which are well known in the art. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made

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to attach the tethers recited in the claimed invention of the '818 patent to the substrate using standard immobilization chemistries which are well known in the art, including cyanogen bromide, succinimide, aldehydes, tosyl chloride, avidin-biotin, epoxide, and maleimides, because the claims of the '818 patent require covalent attachment yet are not limited to any particular attachment agents and because it is routine to use standard immobilization chemistries which are well known in the art to achieve only the expected immobilization because of their familiarity and predictability to the artisan.

Claims 14-16 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264). Herweck et al. disclose a device which can be used for stimulating the growth of eukaryotic blood cells (see Abstract and column 11, lines 24 - 49) and using this device as a "matrix and support upon which cellular matter is grown" (column 11, lines 26 - 27). This device consists of a substrate which can be manufactured from any suitable biocompatible material including fibers and polymers (see column 8, lines 44 - 57). Herweck et al. disclose that the substrate of the device can be shaped in any way needed for its required application (see column 4, lines 21 - 25). This device is also disclosed to be implantable (Abstract, line 1) and useful for treating a patient in need of cell growth (column 4, lines 39 - 40 and claim 28). Herweck et al. also disclose coating the substrate of the device with bioactive material such as platelet derived growth factor, epidermal growth factor, transforming growth factor, erythropoietin, and fibroblast growth factor (see claim 25 and column 12, lines 1 - 35). Herweck et al. achieve an enhanced rate of target cell growth, i.e. growth of cells at the implantation site is enhanced compared to if no implantation had been made, and certain factors which can be present stimulate, i.e. enhance, endothelial cell growth

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(column 6, lines 23-29 and 33-36). Herweck et al. do not disclose biocompatible tethers which have one end covalently linked to the substrate and a growth effector molecule covalently linked to the other end. Merrill discloses star molecules composed of biocompatible, non-thrombogenic, water-soluble polyethylene oxide (PEO)(see Abstract and column 1, line 21) which can have one arm covalently linked to a substrate thereby anchoring the molecule (see column 2, lines 11 - 14) and another arm covalently linked to a bioactive molecule (see column 5, lines 3 - 8 and claim 15). The same tresyl chloride attachment agent can be used to attach the star molecule to the substrate and to the bioactive molecule (see, e.g., column 4, lines 7-9 and 61-64, and claims 10-16). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a composition for use in stimulating the growth of eukaryotic blood cells consisting of a biocompatible substrate, biocompatible tethers and growth effector molecules as described by Herweck et al. using the polyethylene oxide star molecules for the biocompatible tether components as described by Merrill because the star molecules will prevent thrombogenesis from occurring when the device of Herweck et al. is implanted while still ensuring that the device remains coated with the bioactive material. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the tresyl chloride attachment agent of Merrill to attach the biocompatible substrate and the growth effector molecules of Herweck et al to the biocompatible tethers because Merrill discloses tresyl chloride to be a useful attachment means, and the use of tresyl chloride as the attachment means would not have been expected to affect adversely the functioning of Herweck et al's bioactive materials.

Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck et al. in view of Merrill (U.S. Patent No. 5,171,264) as applied against claims 14 - 16 and 33 above, further in view of Mikos. Neither Herweck et al. nor Merrill disclose a substrate which is biodegradable. Mikos discloses a "biodegradable, bioresorbable , three-dimensional template for repair and replacement of diseased or injured bone which provides mechanical strength to bone while also providing a guide for growth of bone tissue" (see Abstract, lines 1 - 4). Mikos discloses that "the implant is seeded with osteoblasts prior to implantation to provide regeneration sites for bone tissue" (see column 1, lines 64 - 63). It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to make a cell growth composition outlined in the above rejection using a biodegradable material as described by Mikos because a patient in need of an implantable cell growth composition might only need it for a defined period of time and it would be less deleterious to the patient and more conducive to overall healing to have the cell growth composition biodegrade and be bioabsorbed so that further surgery and trauma to the patient would not be necessary.

(11) *Response to Argument*

Appellants contend: (1) that Herweck et al do not suggest that it would be advantageous to tether growth factors to the substrate, and Merrill does not suggest using star molecules for tethering growth effector molecules to a substrate; (2) that Herweck et al and/or Merrill do not suggest attaching growth effector molecules in a concentration and with tethers so that the rate of cell growth is enhanced over the rate of cell growth with soluble growth effector molecules or growth effector molecules adsorbed to a substrate; (3) that Merrill teaches away from the claimed compositions and methods because its PEO star molecules are disclosed to be non-

thrombogenic and would thus have been expected to repel cells; (4) that Mikos does not teach tethering growth effector molecules to a biodegradable substrate, and only with hindsight would Mikos, Merrill, and Herweck et al be combined; and (5) that a two-way obviousness test is appropriate for the proposed obviousness-type double patenting rejections where subsequently-filed applications have issued first through no inventor or assignee fault.

In section (8)(A) of the Brief, entitled “The Claimed Invention”, there is much discussion of various aspects of the invention, such as “the polymers of the claimed compositions and methods are soluble in aqueous solution and will extend to their full length, providing a wide range of movement (flexibility) to the factors attached thereto” (Brief at page 7, lines 2-4); that the tethers do not interact with the cell (Brief at page 7, lines 10-11); that the use of branched tethers avoids the potential problem of discouraging cell growth while minimizing the amount of tether material (Brief at page 7, lines 20-21); that Appellants have avoided sterically hindering contact of growth effector molecules with the receptors in the cell membrane (Brief at page 8, lines 1-2); that Appellants can go to very low factor concentrations and still achieve receptor aggregation by virtue of having more than one factor on each tether (Brief at page 9, lines 5-6); that the tethers can be very far apart (Brief at page 9, lines 6-7); and that Appellants’ tethers can bind more than one molecule of the same growth effector or can bind different growth effector molecules, and the density of the growth effector molecule on a substrate can be increased without substantially increasing the number of cell-repellant tethers (Brief at page 9, lines 15-17). However, none of these aspects of Appellants’ invention is recited in the claims, and patentability must be based upon claimed, not unclaimed, differences over the prior art. These unclaimed aspects of the invention are mentioned elsewhere in Appellants’ Brief, e.g., at page

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12, lines 17-19, and page 14, lines 3-4, and again can not be relied upon to distinguish over the prior art.

With respect to contention (1), while the examiner agrees that Herweck et al do not suggest that it would be advantageous to tether the factors to the substrate, and that Merrill does not suggest using the star molecules for tethering growth effector molecules to a substrate, it is only to be expected in an obviousness rejection combining references that each of the references does not teach or suggest some aspect of the claimed invention. Obviousness based upon the combination of Herweck et al with Merrill does not require Herweck et al or Merrill expressly to state their combination with the other patent. Rather, obviousness must be determined on the basis of the prior art when considered as a whole, not on the basis of any single reference, and the teaching, suggestion, or motivation to combine references under 35 U.S.C. 103 can be implicit rather than explicit. See MPEP 2143.01. Merrill teaches that the bioapplications contemplated for its immobilized polyethylene oxide star molecules include biomedical applications in which blood contact is involved, e.g., intravenous catheters and implantable vascular prostheses (see, e.g., column 2, lines 17-23). While Merrill's "primary use" may be in protein separations and purifications, this is not relevant to the rejection because all the disclosure of a reference, not just the reference's preferred embodiments, must be considered in determining prima facie obviousness. See MPEP 2123. Merrill discloses polyethylene oxide star molecules which can be simultaneously covalently linked to a substrate and to a bioactive molecule and which can be used to coat biomedical devices to be used in vivo to prevent thrombosis at the locations of the device. Merrill teaches that its immobilized polyethylene oxide star molecules have the beneficial property of being non-thrombogenic. Because Herweck

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et al's implants will also be in blood contact, thrombogenesis will be a concern for Herweck et al, and Merrill provides a solution for avoiding thrombogenesis while still permitting Herweck et al's implants to remain coated with bioactive material. Because it is desirable in the art to prevent thrombosis, it would be desirable to coat the biomedical device of Herweck et al with the polyethylene oxide of Herweck et al.

With respect to contention (2), Herweck et al in combination with Merrill is deemed to suggest enhanced cell growth without internalization. Herweck et al already teach an enhanced rate of target cell growth, i.e. growth of cells at the implantation site is enhanced compared to if no implantation had been made (see column 6, lines 23-29 and 33-36). This is not an aspect of Appellants' claimed invention which is missing from Herweck et al and which needs to be supplied by the secondary reference. Tethering of the bioactive materials of Herweck et al through the polyethylene oxide of Merrill would still result in the bioactive materials being present at the implantation site, and therefore an enhanced rate of growth would have been expected to be maintained. It is apparent to one of ordinary skill in the art that covalent tethering of a bioactive material to a substrate, which is significantly larger than any cell which will come into contact with the substrate, will prevent internalization of the bioactive material by cells. Note that motivation to combine references under 35 U.S.C. 103 need not be the same as Appellants' motivation. See MPEP 2144. Accordingly, in order to establish prima facie obviousness, the examiner need not establish that it is obvious to combine Herweck et al and Merrill for the express purpose of preventing internalization of growth effector molecules or of enhancing the rate of target cell growth.

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There is no evidence of record showing that there is any criticality in the concentration of growth effector molecules needed to achieve the enhanced rate of target cell growth recited in the appealed claims. In the only comparative example, Figure 2 of the specification reports experiments in which adsorbed but untethered EGF at a concentration of 1.9 ng/cm² results in a lower rate of DNA synthesis than tethered EGF at a concentration of 5 ng/cm². However, it is only to be expected that a higher concentration of EGF results in a higher rate of cell growth. Because of the significant difference in EGF concentrations between the two experiments, it is not possible to conclude that the increase in the cell growth is a result of the tethering. The critical concentration alleged by Appellants is unproven.

With respect to contention (3), Merrill at column 1, lines 6-9, states that polyethylene oxide "does not absorb proteins of the intrinsic clotting system nor of the platelet membrane". This does not mean, as concluded by Appellants, that POE repels cells, because repulsion is not the negation of absorption and the POE may merely be inert with respect to cells. It also does not follow, merely because polyethylene oxide does not absorb proteins of the intrinsic clotting system nor of the platelet membrane, that all cells would necessarily be repelled. Platelets are only one type of the many different cells found in vivo, and in particular are not the type of cells whose growth Herweck et al intend to promote with their implant (see, e.g., column 11, lines 24-49). Even assuming that the POE of Merrill did repel platelets, this is preferable in its combination with Herweck et al which desires blood circulation through the implant and not clotting (column 11, lines 24-27). There is no evidence of record and no reason to believe that the polyethylene oxide of Merrill would prevent the bioactive materials of Herweck et al from interacting with and stimulating cells which comprise receptors for the bioactive materials.

At page 14, second full paragraph, of the Brief, Appellants comment that the references do not “lead one of ordinary skill in the art to have a reasonable expectation that the claimed method could be used as defined by claim 34.” However, it should be noted that claim 34 is not rejected over the prior art of record, including Herweck et al, Merrill, and Mikos. Claim 34 is grouped separately from the claims which are rejected under 35 U.S.C. 103 (see section (7) of the Brief), and the nonobviousness of claim 34 does not mandate any conclusion as to the obviousness of claims 14-16 and 33.

With respect to contention (4), the examiner agrees that Mikos does not teach tethering growth effector molecules to a biodegradable substrate. The examiner relies upon Herweck et al and Merrill to provide motivation and suggestion to tether a growth effector molecule to a substrate. However, there is motivation to combine Mikos with Herweck et al and Merrill because of the expected benefit of using a biodegradable material which would only be present in vivo for a defined period of time and which would be less deleterious to the patient and more conducive to overall healing.

With respect to contention (5), Appellants’ Brief does not set forth the appropriate test for when two-way obviousness is necessary. The appropriate test is set forth, e.g., in Appellants’ response filed August 21, 2002, at page 9, last full paragraph; in MPEP 804(II)(B)(1)(b), second sentence; and in *In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998): A two-way test is to be applied only when the applicant could not have filed the claims in a single application and there is administrative delay. Note that the court in Berg emphasizes that the first condition is a question of written description, i.e. the issue is whether the disclosure of the first application supports the second set of claims (see Berg at page 1233, second full paragraph). The fact situation in *In re*

Braat, 19 USPQ2d 1289 (Fed. Cir. 1991) is distinguished because in Braat, the later filed application was a continuation-in-part of the first-filed application, and the first-filed application did not support the claims of the later-filed application (see Berg, paragraph bridging pages 1230 and 1231). In the instant situation, the claims of the later filed applications, which issued as U.S. Patent Nos. 5,906,828 and 6,045,818, are necessarily supported by this first-filed application because the later filed applications are continuations, not continuations-in-part, of this first-filed application. The specifications of all three applications are identical as in Berg and in contrast with Braat (see Berg at page 1231, first full paragraph). Further, to require two-way obviousness in this situation, a policy concern of the court in *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993) would be violated: "By adopting the easy course of filing a continuation or divisional application to gain a narrow claim, a patentee could gain an extension of the term on a species when the broader genus later issued. This practice would extend the exclusionary right past the 17-year limit mandated by Congress." Goodman at page 2016, fourth full paragraph.

Because the first condition for two-way obviousness has not been met, it is not necessary to consider the second condition, i.e. who actually controlled the respective rates of prosecution. Compare Berg at page 1232, first full paragraph. In any event, the previous appeal in which rejections of 27 of 32 appealed claims were affirmed does not constitute an undue administrative delay which requires application of a two-way obviousness test.

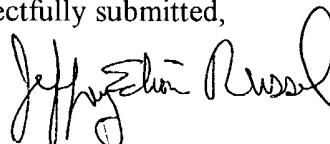
The examiner agrees with Appellants that if a two-way obviousness test is the appropriate standard for the obviousness-type double patenting rejections, then the rejections should be withdrawn because the claims of U.S. Patent Nos. 5,906,828 and 6,045,818 are unobviousness over the instant claims. If a one-way obviousness test is the appropriate standard for the

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obviousness-type double patenting rejection, it is noted that Appellants have not traversed the examiner's arguments of one-way obviousness as set forth in the rejections.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,




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April 15, 2004




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